Breast Cancer Res Treat (2012) 134:363–370
DOI 10.1007/s10549-012-2031-7

EPIDEMIOLOGY

Breast cancer incidence trends in European women aged 20–39 years at diagnosis

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Received: 6 January 2012 / Accepted: 12 March 2012 / Published online: 29 March 2012

Abstract An increase in the incidence of breast cancer in women aged <40 years has been reported in recent years. Increased incidence could be partly explained by subtle detection biases, but the role of other risk factors cannot be ruled out. The purpose of the present study was to investigate the changes in temporal trends in breast cancer incidence in European women aged 20–39 years at diagnosis. Age specific breast cancer incidence rates for 17 European Cancer Registries were retrieved for the calendar period 1995–2006. Cancer registries data were pooled to reduce annual fluctuations present in single registries and increase incidence rates stability. Regression models were fitted to the data assuming that the number of cancer cases followed the Poisson distribution. Mean annual changes in the incidence rate (AIC) across the considered time window were calculated. The AIC estimated from all European registries was 1.032 (95 % CI = 1.019–1.045) and 1.014 (95 % CI = 1.010–1.018) in women aged 20–29 and 30–39 years old at diagnosis, respectively. The major change was detected among women aged 25–29 years at diagnosis: AIC = 1.033 (95 % CI = 1.020–1.046). The upward trend was not affected when registries with high or low AIC were removed from the analysis (sensitivity analysis). Our findings support the presence of an increase in the incidence of breast cancer in European women in their 20s and 30s during the decade 1995–2006. The interpretation of the observed increase is not straightforward since a number of factors may have affected our results. The estimated annual increase in breast cancer incidence may result in a burden of the disease that is important in terms of public health and deserves further investigation of possible risk factors.

Keywords Breast cancer · Incidence · Time trend · Young women

The members of AIRTUM Working Group are given in Appendix.

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Introduction

Breast cancer is the most common form of cancer in women in most parts of the world, especially in the industrialized areas [1]. In Europe, it accounts for about 30 % of all incident tumors in females [2], with rates ranging from about 40/100,000 in Lithuania and Poland, to 75/100,000 in Norway, and to over 90/100,000 in the Netherlands and some Italian areas [3]. Overall, the annual breast cancer incidence had been increasing worldwide during the last century [4–6], but a downturn in tumor incidence was observed in the 2,000s among women older than 45–50 years at diagnosis in the United States, possibly

in relation to the decrease in the use of hormone replacement therapy [7, 8], and in some European countries [9–13] In the meantime, a number of European cancer registries had started to report an upward trend, since the 1990s, among women aged <40 years. The average annual increase between 1995 and 2004 ranged between 2 % in the Eindhoven cancer registry, south eastern Netherlands [14] and 8.7 % in the Canton of Geneva where a particularly marked increase (46.7 %) was observed during the triennium 2002–2004 [15]. In general, these registry specific statistics are based on small numbers of cases per year observed in young women, with an inevitable high degree of variability and should be interpreted with caution. However, the increase of 1.3 % per year in invasive breast cancer incidence between 1992 and 2004 among US white women younger than 40 years at diagnosis is based on large number of cases and cannot be considered as the result of a chance fluctuation [16].

The aim of this study was to investigate the existence in Europe of a recent increase in the incidence of invasive breast cancer in women aged <40 years at diagnosis by exploring age-specific temporal trends in pooled incident data from European population-based cancer registries.

Methods

Data from 17 European population-based registries that had uninterrupted registration for at least 5 years over the period 1995–2006 were used to evaluate overall and age-specific incidence changes of invasive breast cancer in women aged 20–39 years at diagnosis. Yearly based breast cancer incident cases were available on a national basis for 12 registries and referred to cities or counties for the others (Table 1). Data were extracted between October and December 2009 from the registry websites for the registries of Belgium, Czech Republic, Ireland, the Netherlands, Scotland, Bremen, Saarland, and Schleswig–Holstein. The database of the Association of the Nordic Cancer Registries (NORDCAN) [17] was used to retrieve incidence data for the Danish, Finnish, Icelandic, Norwegian, and Swedish registries. Incidence data were directly provided for the Cancer Registry of Croatia, Slovenia, and Geneva (Switzerland). The Italian Association of Cancer Registries (AIRTUM) provided data for the county registries of Modena, Parma, Reggio Emilia, and Naples. Data were available for the following periods: 1995–2006 for the registries of Croatia, Denmark, Finland, Geneva, Iceland,

Table 1 European cancer registries demographic items, and website

Registry	Identifier	Female population*	Population coverage	Website
Belgian Cancer Registry	Belgium	1,425,726	Belgium	http://www.kankerregister.org
Bremen Cancer Registry	Bremen	91,462	Land Bremen (DE)	http://www.krebsregister.bremen.de
Croatian National Cancer Registry	Croatia	634,590	Republic of Croatia	http://www.hzjz.hr/cancer
Czech National Cancer Registry	Czech	1,511,081	Czech Republic	http://www.uzis.cz
Danish Cancer Registry	Denmark	740,151	Denmark	http://www.ancr.nu/nordcan.asp
Finnish Cancer Registry	Finland	667,779	Republic of Finland	http://www.ancr.nu/nordcan.asp
Geneva Cancer Registry	Geneve	65,578	Canton of Geneva (CH)	http://www.asrt.ch
Icelandic Cancer Registry	Iceland	41,626	Republic of Iceland	http://www.ancr.nu/nordcan.asp
The Irish National Cancer Registry	Ireland	593,666	Republic of Ireland	http://www.ncri.ie
Italian Cancer Registries	Italy	290,711	4 Italian areas**	http://www.registri-tumori.it
National Netherlands Cancer Registry	Netherlands	2,310,413	The Netherlands	http://www.ikcnet.nl
Cancer Registry of Norway	Norway	630,346	Norway	http://www.ancr.nu/nordcan.asp
Cancer Registry Saarland	Saarland	140,952	Land Saarland (DE)	http://www.krebsregister.saarland.de
Cancer Registry Schleswig–Holstein	Schleswig–Holstein	359,088	Land Schleswig–Holstein (DE)	http://www.krebsregister-sh.de
Scottish Cancer Registry	Scotland	729,841	Scotland	http://www.isdscotland.org
Cancer Registry of Slovenia	Slovenia	292,055	Republic of Slovenia	http://www.onko-i.si
Swedish Cancer Registry	Sweden	1,159,781	Sweden	http://www.ancr.nu/nordcan.asp

* Age group 20–39

** Counties of Parma, Modena, Reggio Emilia, and Naples' Local Health Unit 4

Ireland, the Netherlands, Norway, Saarland, Scotland, Slovenia, and Sweden; 1995–2005 for Belgium and Italy; 1998–2006 for Bremen and the Czech Republic; and 1999–2006 for Schleswig–Holstein. The number of female invasive breast cancer cases (i.e., code C50 of the 10th revision of the International Classification of Diseases, ICD-10) and the population at risk, available (or computed from the incidence rates) for quinquennial age groups (20–24, 25–29, 30–34, and 35–39 years old at diagnosis) and calendar year were collected for each registry. Pooling cancer registries and age-groups data was necessary (i.e., 20–29 and 30–39) to insure adequate age- and calendar year-specific numbers of breast cancer cases per year and obtain more stable and reliable estimates incidence rates, by reducing variability due to small numbers of observed cases.

Statistical methods

In order to insure internal comparability, cancer rates were standardized by age (5-year groups) using the age specific European standard population structure. Regression models were fitted to the data assuming that the number of cancer cases followed the Poisson distribution [18]. Between countries, variability in cancer rates (i.e., heterogeneity), was accounted for by fitting a random effect model to the data [19], including the number of incident cases observed each year in each registry as dependent variable and year of diagnosis and age as predictors. Registry was included in the model as the clustering variable and the population at risk of each registry was used as a weight for the parameter estimates.

Such model allowed to estimate the amount of heterogeneity present in the data and provided more efficient estimates of the standard errors of the model parameters. In the presence of over dispersion, i.e., when data exhibit more residual variability than expected according to the Poisson model, the negative binomial distribution (NBD) was applied to the data [18]. The NBD variance function is: $V(\mu) = \mu + \varphi\mu^2$, where μ is the NBD mean and φ is the over-dispersion parameter. When φ tends to zero, NBD reduces to the Poisson distribution. The regression parameters estimated by both models are interpretable as the average annual incidence change (AIC), which is the estimated mean annual change in the incidence rate across the considered time window 1995–2006. To describe the observed pattern of the age standardized incidence rates, the Lowess smoothing method was applied [20]. To estimate the heterogeneity of the AICs across the age groups, the interaction term age at diagnosis-year of diagnosis (both considered as continuous variables) was added to the regression model. The coefficient of the interaction term describes the AICs change across age groups. Moreover, sensitivity analysis was performed to investigate the influence of data from individual cancer registries on the AIC estimated when all registries are included in the analysis. Sensitivity analysis was done by the leaving-one-out method that consists in the computation of a set of regression coefficients, each corresponding to leaving one of the 17 cancer registries out of the calculation. STATA software [21] was used for the statistical analysis and the generation of sensitivity plots.

Results

The AIC estimated for each cancer registry in European women aged 20–29 and 30–39 years at diagnosis across the time period 1995–2006 is shown in Table 2. The pooled age-specific AIC estimated from all European registries was 1.032 (95 % CI = 1.019–1.045) and 1.014 (95 % CI = 1.010–1.018) in women aged 20–29 and 30–39 years at diagnosis, respectively (Table 2).

Table 3 shows the AIC estimated from pooled incidence data for quinquennial age groups. The increase observed during the considered time window was common to all age groups and the major AIC change was detected among women aged 20–24 and 25–29 years at diagnosis: AIC = 1.021 (95 % CI = 0.984–1.059) and 1.033 (95 % CI 1.020–1.046), respectively. The estimated AIC decreased with increasing age at diagnosis (p trend = 0.008). The temporal pattern of the incidence rates for women aged 20–29 and 30–39 years at diagnosis across the time window 1995–2006 for the pooled cancer registries is depicted in Fig. 1. The contribution of each registry to the AIC estimated from pooled European data among women aged 20–29 and 30–39 years at diagnosis (sensitivity analysis) is shown in Fig. 2. The size of the AIC-estimated upward trend was not radically modified when any of the registries with the largest AIC was removed from the analysis in the age group 20–29 years and remained statistically significant. In women aged 30–39 years at diagnosis, the exclusion of the Belgian registry resulted in an AIC = 1.0098 (95 % CI = 1.006–1.014).

Discussion

Worldwide, the incidence of breast cancer has shown a dramatic geographic and temporal variability. A strong increase was observed during the 20th century, first in industrialized western countries, and eventually in several eastern countries. When cohort effects were taken into account, this increase appeared to similarly affect all age groups [22]. During the last decades of the century, a further increase was reported in women aged 50–69 years [23] and to a lesser extent in women under 49 years [24,

Table 2 Annual incidence change (AIC) in European women aged 20–29 and 30–39 year at diagnosis across the time period 1995–2006 by cancer registries and age groups

	Age at diagnosis					
	20–29 years			30–39 years		
Cancer registry	Cases	AIC	95 % CI	Cases	AIC	95 % CI
Belgium	389	1.043	0.924–1.176	3,842	1.046	0.989–1.107
Bremen	18	1.066	0.851–1.335	167	0.982	0.897–1.075
Croatia	104	1.109	0.987–1.247	979	1.027	0.957–1.102
Czech Republic	199	1.091	0.926–1.285	1488	1.027	0.947–1.114
Denmark	148	1.011	0.907–1.127	1,751	1.008	0.959–1.058
Finland	134	1.009	0.894–1.139	1,515	0.998	0.943–1.056
Geneva	18	1.141	0.958–1.358	173	1.045	0.993–1.101
Iceland	10	1.135	0.844–1.525	90	1.038	0.955–1.129
Ireland	129	1.012	0.903–1.133	1,384	1.010	0.954–1.068
Italy	93	1.027	0.903–1.167	882	0.983	0.918–1.053
Netherlands	677	1.021	0.928–1.123	7,495	1.014	0.968–1.063
Norway	95	1.101	0.976–1.242	1,286	1.002	0.947–1.060
Saarland	22	0.989	0.853–1.147	377	0.998	0.943–1.056
Schleswig–Holstein	51	0.967	0.784–1.192	852	0.998	0.915–1.089
Scotland	155	0.984	0.872–1.110	2,085	1.007	0.958–1.059
Slovenia	57	0.945	0.850–1.051	560	1.021	0.969–1.076
Sweden	224	1.050	0.940–1.174	2,490	1.006	0.958–1.057
Pooled registries*	2,523	1.032	1.019–1.045	27,416	1.014	1.010–1.018

* AIC adjusted for heterogeneity evaluated using the random effect change-point Poisson model

Table 3 Quinquennial age specific annual incidence changes (AIC) and their 95 % confidence intervals (95 % CI) in European breast cancer incidence rates (pooled European cancer registry data) adjusted for heterogeneity across the time period 1995–2006

Age group (years)	Cases	AIC	95 % CI	*p*
20–24	324	1.021	0.984–1.059	0.261
25–29	2,199	1.033	1.020–1.046	<0.001
30–34	8,004	1.019	1.011–1.026	<0.001
35–39	19,412	1.012	1.007–1.017	<0.001

Linear trend estimated using the random effect change-point Poisson model

AIC trend across age groups: log-likelihood ratio test, $p_{trend} = 0.008$

25] followed in the early 2000s by a reversal in several European areas and in the United States [26]. These fluctuations are considered to be mainly attributable to the increased uptake and subsequent saturation of mammographic screening [27–29] and to temporal changes in the proportion of women using hormone-replacement therapy (HRT) [8, 26, 30].

Conversely, few analyses are available on the behavior of invasive breast cancer incidence in women under the age of 40 or 30. Information is limited by the small series of patients studied (approximately 7 % of women with breast cancer are diagnosed before the age of 40 years) and by the different age cut-off used by various authors when defining "young women" (<35, <40, <45, and <50 years of age) [31, 32]. Recently, some European cancer registries reported increased incidence rates for breast cancer in women aged <40 years at diagnosis. A study carried out in the Canton of Geneva, Switzerland, reported a mean annual incidence increase of 8.7 % (95 % CI = 2.8–15.0) between 1995 and 2004 in women aged 25–39 years at diagnosis, an increase that reached 46.7 % (95 % CI = 7.1–74.0) during the most recent years (i.e., 2002–2004). Although the authors considered also increased surveillance and detection bias as possible explanations for the observed trend, they could not exclude a possible role of exogenous breast cancer risk factors, including those acting in utero and early in life.

Our analysis of breast cancer incidence trends among young women in the period 1995–2006 in 17 European Cancer Registries shows that, in spite of the observed variability in age-specific incidence rates across different geographical regions and the years of observation, breast cancer incidence appears to be increasing by about 3 % and 1 % each year in women aged 20–29 and 30–39 years at cancer diagnosis, respectively. These mean annual increases are statistically significant ($p < 0.001$) and do not appear to be affected by cancer registries with high or low AIC (sensitivity analysis). The largest increase in incident rates (i.e., 3.3 %) was reported among women aged

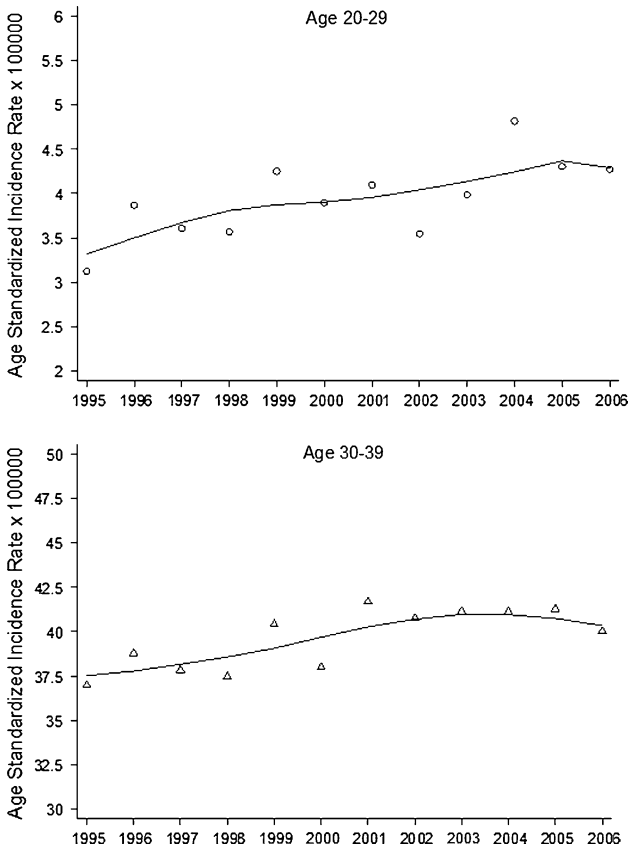

Fig. 1 Lowess smoothed age standardized breast cancer incidence rates among women aged 20–29 and 30–39 years at diagnosis (1995–2006), pooled European registries

25–29 years, and the size of the mean annual increase appeared to diminish with increasing age (p for trend = 0.0084).

Independent support to our findings derives from the increase in breast cancer incidence in young women reported also by other European registries that were not included in our analysis. An increase of the incidence of breast cancer was reported in Spanish women younger than 45 years at diagnosis between 1980 and 2004 (1.7 % per year, 95 % CI 1.3–2.0) [29] and in French women <40 years old (0.65 %, 95 % CI 0.03–1.26), living in seven French Counties (Calvados, Doubs, Hèrault, Isère, Bas–Rhin, Somme and Tarn) during the period 1983–2002 [24]. An uprising trend was observed in the Swiss cancer registries of Vaud and Neuchatel, where, between 1995 and 2005, breast cancer incidence increased of about 2 % in females aged 25–39 years [33]. Overall, these findings suggest the presence of an increase in the incidence of breast cancer in European women in their third and fourth decade of life in recent periods.

The interpretation of the observed increase is not straightforward. First of all, it should be considered whether the increase in incidence is a real one or it is the result of some artifact. Instability due to a low number of incident cases can be ruled out as a possible cause for the observed increase, due to the relatively large number of cases on which these analyses were based, and to the fact that the observed trends were statistically significant. Indeed, in our analyses instability of rates within registries was taken into account by fitting a random effect model to the data to adjust for heterogeneity between registries. The possible link between incidence rates and the estimated annual changes was also evaluated in our analysis by regressing the estimated registry specific AIC toward the observed registry specific median incidence rates. The computed regression coefficient (Fig. 3) was equal to 0.0011 ($p = 0.898$) indicating that the observed mean annual increase did not differ in registries with high and low breast cancer risk.

The observed increase on breast cancer incidence could be also due to varying completeness in the registration of data over the examined time periods. We have included only cancer classified as invasive (code C50, ICD10) and all registries considered in the study operate according to the IARC registration guidelines for quality and completeness. Sensitivity analyses failed to show any significant registry specific effect on the estimated AIC. The degree of under registration reported in Belgium <2004 for the Walloon and Brussels Capital Region [34] may explain the role of Belgium observed in the sensitivity analysis in women aged 30–39. However, despite the reported under registration, breast cancer incidence rates in young women in Belgium were higher than in most of the other registries across the considered time window. Different registration criteria, i.e., inclusion of non invasive cancers or of breast multiple cancers, is unlikely to have influenced our findings. Last but not least, our findings can also be due to chance. However, the significant increase observed across the considered time window and the decreasing AIC with increasing age at diagnosis is suggestive of a real phenomenon.

Conversely, if true, this increase would deserve particular attention because it could represent the consequence of three different phenomena, each one of public health relevance.

(a) It may be the consequence of an increased diagnostic pressure among young European women. Mammography screening programs have increased in Europe in recent years, affecting significantly the detection of breast cancer among women older than 50 years in various European areas. It has been suggested that this may have encouraged the use of mammography also in younger women [33]. It is therefore possible that the observed rise in breast cancer incidence in young women be partially due to the larger use of diagnostic tools such as ultrasonography, mammography, or magnetic resonance imaging outside organized

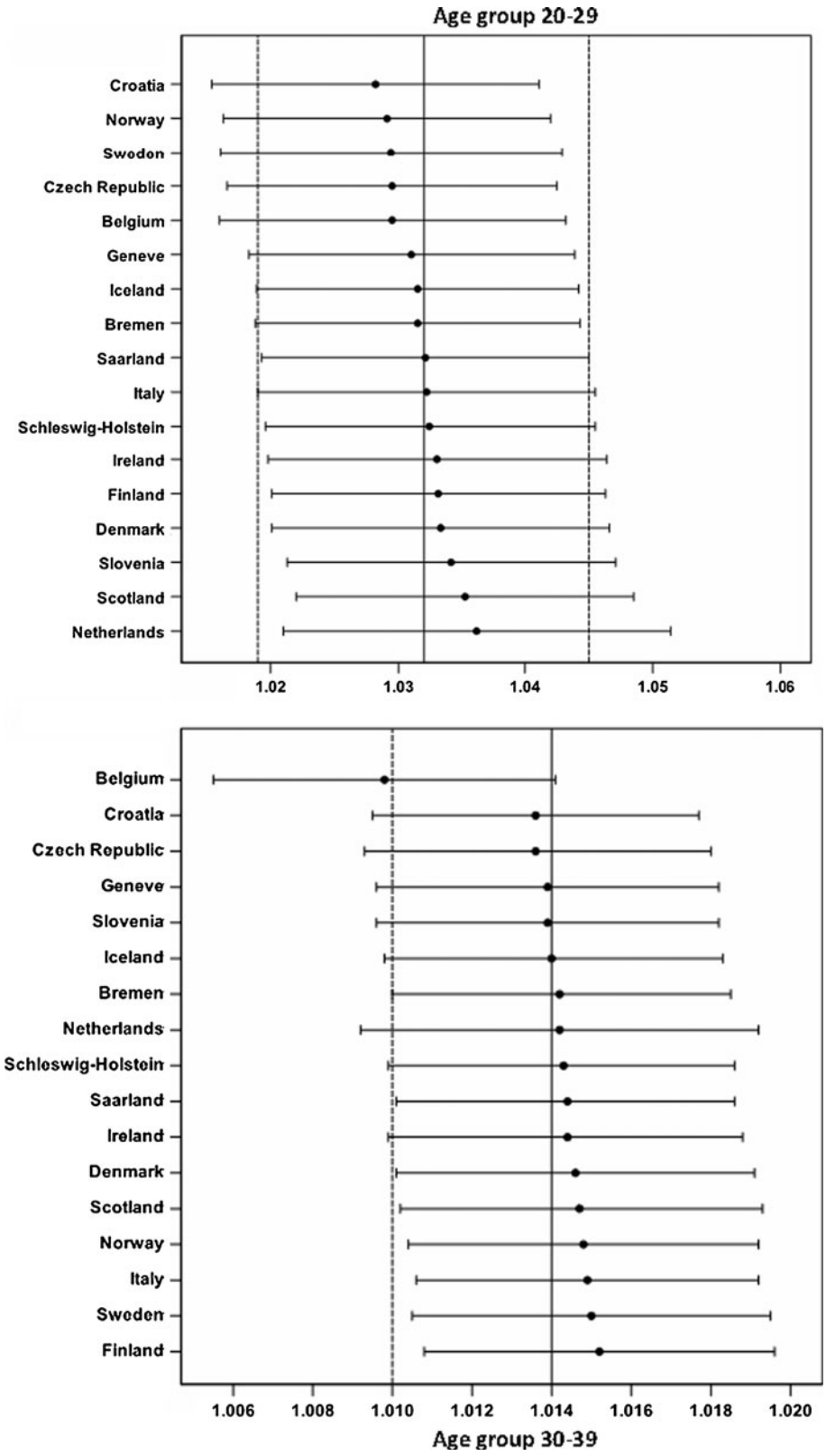

Fig. 2 Sensitivity analysis among women aged 20–29 and 30–39 years old at diagnosis. *Plots* illustrate the effect of each registry on the AIC estimated from the pool of European cancer registry data (AIC *solid vertical line*, 95 % CI *dashed vertical line*). *Dots* indicate the AIC estimated when data from a single registry (*Y* axis) are omitted and *horizontal bars* are the 95 % confidence intervals

screening programs. Nevertheless, such detection bias does not appear as a plausible explanation for our findings, since the increase in the incidence was more marked in women younger than 30 years than in women 30–39 years old at diagnosis, whereas in very young women, due to the low sensitivity of diagnostic

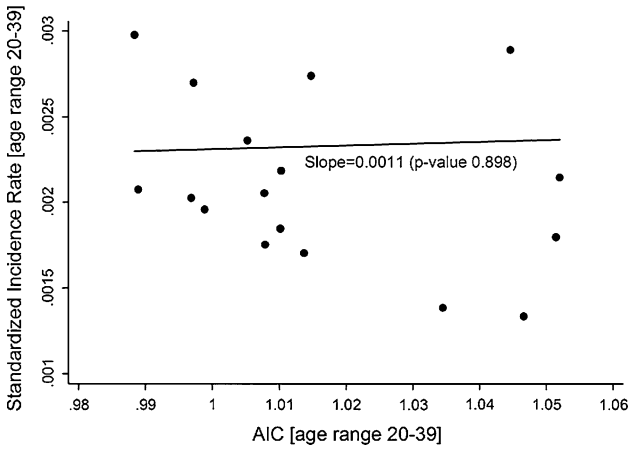

Fig. 3 Relationship between registry specific breast cancer median incidence rates and the estimated annual incidence changes (AIC)

tools and to their less frequent use, the role of diagnostic pressure appears less likely. In addition, as outlined by the authors of the Geneva Registry, if the increase in incidence was due to earlier diagnosis, a change in the stage distribution of cases would be expected, but this was not observed in that register [15]. Under this hypothesis, the incidence in young cohorts should show limited further increases, and should be followed by stable or even decreased incidence rates in older age-groups.

(b) It may be the consequence of a widespread exposure of young European women to factors affecting the risk of premenopausal breast cancer. It is well know that risk factors for pre-and post menopausal breast cancer are not completely overlapping: for instance, obesity is a risk factor only for postmenopausal breast cancer, and before menopause parous women are at higher breast cancer risk than nulliparous women, births at an early age are not protective, and current users of oral contraceptives experience a higher breast cancer risk than never users [13, 35, 36]. If the observed increase is due to factors specifically affecting premenopausal breast cancer risk, it could be expected that similar increases will be experienced by future cohorts of women as they enter the 3rd and 4th decade of life, but the lifetime risk of breast cancer, which depends more strongly on postmenopausal risk, might not result radically modified. Accordingly, research efforts should focus on lifestyle changes experienced by young women such as smoking, increased caloric intake, endogenous hormones, changes in reproductive behavior, history of induced abortion or miscarriage, and hormonal contraceptive use [35]. Although many of these risk factors are not specific to young women, some of them may be more relevant to younger ages [37, 38].

(c) Finally, the reported increase might represent the early signal of a cohort effect, with grave public health consequences in the years to come. In fact, if the estimated annual increase in breast cancer incidence continues over the next 5–10 years, and the increased risk is maintained when these cohorts enter age-groups with much higher breast cancer incidence, the increase in the absolute number of cases could be in the order of several thousands or tens of thousands each year in Europe or in the US, where similar trends in young cohorts have been reported [16]. Which factors might be responsible for this possible cohort effect is impossible to say, even though, beside the already mentioned ones, the roles of in utero exposures or of breast irradiation [37, 39, 40] deserve further investigation.

As a consequence, the behavior of breast cancer incidence should be closely monitored during the next several years, to assess which one, or if more than one, of these three explanations are plausible, allowing projections on the future age-specific incidences of breast cancer in various countries. Second, epidemiological and biological research should concentrate on the identification of the factors which are responsible for these changes in breast cancer incidence. Third, if the incidence of breast cancer in young ages continues to increase, the efficacy of the screening protocols for breast cancer that, on the basis of scanty or no evidence, are currently used in young women and rely on mammography and/or ultrasonography and/or magnetic resonance imaging, should be better assessed. However, considering that the efficacy in young women of these preventive protocols is, at best, limited [41], the development and evaluation of new tools and approaches for primary and secondary prevention of breast cancer in young women represent a priority in cancer research.

Acknowledgments Dr. Luigina Bonelli, Prevenzione Secondaria e Screening, IRCCS AOU San Martino-IST-Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy, for valuable comments.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

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